GenCore version 5.1.9

OM protein - protein search, using sw model

Run on: September 21, 2006, 14:40:07 ; Search time 0.001 Seconds
(without alignments)
984.233 Million cell updates/sec

Title: US-10-668-178-2
Perfect score: 780
Sequence: 1 VRSSSRTPSDXPVAHVVANP.....RPDYLDFAESGQVYFGIIAL 157

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 40 seqs, 6269 residues

Total number of hits satisfying chosen parameters: 40

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 500 summaries

Database : xedit-findpat.subdb:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	773	99.1	157	1	ADH10160	Human tumour necro
2	766	98.2	157	1	AEB45433	TNF-R1 specific hu
3	765	98.1	157	1	AEB45432	TNF-R1 specific hu
4	764	97.9	157	1	AEB45434	TNF-R1 specific hu
5	762	97.7	157	1	AEB45430	TNF-R1 specific hu
6	759	97.3	157	1	AEB45453	TNF-R2 specific hu
7	758	97.2	157	1	AEB45431	TNF-R1 specific hu
8	754	96.7	157	1	AEB45454	TNF-R2 specific hu
9	752	96.4	157	1	AEB45469	TNF-R2 specific hu
10	751	96.3	157	1	AEB45438	TNF-R1 specific hu
11	751	96.3	157	1	AEB45436	TNF-R1 specific hu
12	751	96.3	157	1	AEB45461	TNF-R2 specific hu
13	750	96.2	157	1	AEB45460	TNF-R2 specific hu
14	750	96.2	157	1	AEB45464	TNF-R2 specific hu
15	749	96.0	157	1	AEB45472	TNF-R2 specific hu
16	749	96.0	157	1	AEB45471	TNF-R2 specific hu
17	749	96.0	157	1	AEB45455	TNF-R2 specific hu
18	749	96.0	157	1	AEB45466	TNF-R2 specific hu
19	749	96.0	157	1	AEB45474	TNF-R2 specific hu
20	749	96.0	157	1	AEB45457	TNF-R2 specific hu
21	749	96.0	157	1	AEB45475	TNF-R2 specific hu
22	748	95.9	157	1	AEB45458	TNF-R2 specific hu
23	748	95.9	157	1	AEB45473	TNF-R2 specific hu
24	748	95.9	157	1	AEB45467	TNF-R2 specific hu
25	748	95.9	157	1	AEB45468	TNF-R2 specific hu
26	747	95.8	157	1	AEB45437	TNF-R1 specific hu
27	747	95.8	157	1	AEB45462	TNF-R2 specific hu
28	747	95.8	157	1	AEB45470	TNF-R2 specific hu
29	746	95.6	157	1	AEB45456	TNF-R2 specific hu
30	746	95.6	157	1	AEB45459	TNF-R2 specific hu
31	746	95.6	157	1	AEB45465	TNF-R2 specific hu
32	746	95.6	157	1	AEB45463	TNF-R2 specific hu
33	744	95.4	157	1	AEB45429	TNF-R1 specific hu
34	743	95.3	157	1	AEB45428	TNF-R1 specific hu
35	743	95.3	157	1	AEB45425	TNF-R1 specific hu
36	742	95.1	157	1	AEB45421	Human TNF-alpha mu
37	741	95.0	157	1	AEB45427	TNF-R1 specific hu
38	741	95.0	157	1	AEB45423	Human TNF-alpha mu
39	741	95.0	157	1	AEB45435	TNF-R1 specific hu
40	698	89.5	146	1	AEB45426	TNF-R1 specific hu

ALIGNMENTS

RESULT 1
ADH10160
ID ADH10160 standard; protein; 157 AA.
XX
AC ADH10160;
XX
DT 11-MAR-2004 (first entry)
XX
DE Human tumour necrosis factor variant protein.
XX
KW TNF; tumour necrosis factor; polyethylene glycol; cytostatic; cancer;
KW human; variant.
XX
OS Homo sapiens.
XX
PN EP1354893-A2.
XX
PD 22-OCT-2003.
XX
PF 30-JAN-2003; 2003EP-00250587.
XX
PR 25-MAR-2002; 2002JP-00083509.
PR 26-JUN-2002; 2002JP-00185387.
XX
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU.
PA (MAYU/) MAYUMI T.
PA (TSUT/) TSUTSUMI Y.
PA (NAKA/) NAKAGAWA S.
XX
PI Mayumi T, Tsutsumi Y, Nakagawa S, Ikegami H;
XX
DR WPI; 2004-063952/07.
DR N-PSDB; ADH10169.
XX
PT A physiologically active complex which comprises a protein part with
PT tumor necrosis factor activity and a high molecular part has higher
PT stability and retention in living bodies and is useful to treat disease,
PT particularly cancer.
XX
PS Example 1; SEQ ID NO 3; 18pp; English.
XX
CC The present sequence represents a physiologically active complex which
CC comprises a proteinaceous part with tumour necrosis factor (TNF) activity
CC and a high molecular part bound artificially to the N-terminus of the
CC proteinaceous part. The proteinaceous part comprises the sequence
CC selected from ADH10159 and the molecular part has a molecular weight of
CC 500-5000 Da and is a homopolymer of polyethylene glycol or a copolymer of
CC ethylene glycol and its derivatives. The invention is used to treat
CC susceptive disease, particularly cancer. The complex has a higher
CC stability and longer retention time in living bodies than intact tumour
CC necrosis factor. The present sequence represents a human TNF variant
CC protein.
XX
SQ Sequence 157 AA;

Query Match 99.1%; Score 773; DB 1; Length 157;
Best Local Similarity 96.2%; Pred. No. 0;
Matches 151; Conservative 0; Mismatches 6; Indels 0; Gaps 0;

Qy 1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

```
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 2
AEB45433
ID   AEB45433 standard; protein; 157 AA.
XX
AC   AEB45433;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:17.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45447.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 17; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             98.2%;  Score 766;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    1;  Mismatches    7;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||: ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFADDGQVYFGIIAL 157


RESULT 3
AEB45432
ID   AEB45432 standard; protein; 157 AA.
XX
AC   AEB45432;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:16.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45446.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
```

```
XX
PS   Claim 4; SEQ ID NO 16; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             98.1%;  Score 765;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    1;  Mismatches    7;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||| |:||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFRETGQVYFGIIAL 157


RESULT 4
AEB45434
ID   AEB45434 standard; protein; 157 AA.
XX
AC   AEB45434;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:18.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45448.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 18; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             97.9%;  Score 764;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    0;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||| ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFANDGQVYFGIIAL 157


RESULT 5
AEB45430
ID   AEB45430 standard; protein; 157 AA.
XX
AC   AEB45430;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:14.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
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KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45444.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 14; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             97.7%;  Score 762;  DB 1;  Length 157;
  Best Local Similarity   94.3%;  Pred. No. 0;
  Matches  148;  Conservative    2;  Mismatches    7;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||| ::||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFKDTGQVYFGIIAL 157


RESULT 6
AEB45453
ID   AEB45453 standard; protein; 157 AA.
XX
AC   AEB45453;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:37.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45476.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 37; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
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CC  The sequence data for this patent did not form part of the printed
CC  specification, but was obtained in electronic format directly from WIPO
CC  at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ  Sequence 157 AA;

  Query Match             97.3%;  Score 759;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    0;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||| || ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWQNRWANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 7
AEB45431
ID  AEB45431 standard; protein; 157 AA.
XX
AC  AEB45431;
XX
DT  22-SEP-2005  (first entry)
XX
DE  TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:15.
XX
KW  tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW  autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW  acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW  plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW  antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW  antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW  vasotropic; cerebroprotective; dermatological; immunomodulator;
KW  antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW  mutein.
XX
OS  Homo sapiens.
OS  Synthetic.
XX
PN  WO2005066206-A1.
XX
PD  21-JUL-2005.
XX
PF  05-JAN-2005; 2005WO-JP000032.
XX
PR  06-JAN-2004; 2004JP-00001427.
XX
PA  (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA  (MAYU/) MAYUMI T.
PA  (TSUT/) TSUTSUMI Y.
PA  (NAKA/) NAKAGAWA S.
XX
PI  Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR  WPI; 2005-506850/51.
DR  N-PSDB; AEB45445.
XX
PT  Novel tumor necrosis factor TNF mutant protein, useful for treating
PT  and/or preventing diseases such as inflammation, and other diseases
PT  caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT  rheumatoid arthritis, allergy.
XX
PS  Claim 4; SEQ ID NO 15; 34pp; Japanese.
XX
CC  The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC  particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC  TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC  a TNF mutant protein comprising an amino acid sequence derived from the
CC  human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC  one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC  N-terminus, and amino acid residues at positions 84-89 by other amino
CC  acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC  mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC  protein. The TNF mutant proteins are useful for treating and/or
CC  preventing diseases such as inflammation, and other diseases caused by
CC  overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC  cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC  Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC  transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC  respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC  lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC  etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC  represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC  The sequence data for this patent did not form part of the printed
CC  specification, but was obtained in electronic format directly from WIPO
CC  at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ  Sequence 157 AA;

  Query Match             97.2%;  Score 758;  DB 1;  Length 157;
  Best Local Similarity   94.3%;  Pred. No. 0;
  Matches  148;  Conservative    0;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||    ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFRTDGQVYFGIIAL 157


RESULT 8
AEB45454
ID  AEB45454 standard; protein; 157 AA.
XX
AC  AEB45454;
XX
DT  22-SEP-2005  (first entry)
XX
DE  TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:38.
XX
KW  tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW  autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW  acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW  plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW  antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW  antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW  vasotropic; cerebroprotective; dermatological; immunomodulator;
KW  antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW  mutein.
XX
OS  Homo sapiens.
OS  Synthetic.
XX
PN  WO2005066206-A1.
XX
PD  21-JUL-2005.
XX
PF  05-JAN-2005; 2005WO-JP000032.
XX
PR  06-JAN-2004; 2004JP-00001427.
XX
PA  (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA  (MAYU/) MAYUMI T.
```

```
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45477.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 38; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.7%;  Score 754;  DB 1;  Length 157;
  Best Local Similarity   94.3%;  Pred. No. 0;
  Matches  148;  Conservative    0;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWTNGYANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 9
AEB45469
ID   AEB45469 standard; protein; 157 AA.
XX
AC   AEB45469;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:53.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45492.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 53; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.4%;  Score 752;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  ||   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITKSYSKPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
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RESULT 10
AEB45438
ID   AEB45438 standard; protein; 157 AA.
XX
AC   AEB45438;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:22.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45452.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 22; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.3%;  Score 751;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    ||  ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIGGPYQRPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 11
AEB45436
ID   AEB45436 standard; protein; 157 AA.
XX
AC   AEB45436;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:20.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45450.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 20; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
```

```
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.3%;  Score 751;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||   |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAPGYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 12
AEB45461
ID   AEB45461 standard; protein; 157 AA.
XX
AC   AEB45461;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:45.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45484.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 45; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.3%;  Score 751;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    3;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||: :| : ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISSAYASPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 13
AEB45460
ID   AEB45460 standard; protein; 157 AA.
XX
AC   AEB45460;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:44.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
```

```
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45483.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 44; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.2%;  Score 750;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||: :|   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISYNYNGPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 14
AEB45464
ID   AEB45464 standard; protein; 157 AA.
XX
AC   AEB45464;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:48.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45487.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 48; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.2%;  Score 750;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;
```

```
Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  :|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITTAYSGPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 15
AEB45472
ID   AEB45472 standard; protein; 157 AA.
XX
AC   AEB45472;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:56.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45495.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 56; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  :|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISKTYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 16
AEB45471
ID   AEB45471 standard; protein; 157 AA.
XX
AC   AEB45471;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:55.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45494.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
```

```
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 55; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    | : ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITPGYPSPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 17
AEB45455
ID   AEB45455 standard; protein; 157 AA.
XX
AC   AEB45455;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:39.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45478.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 39; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||| |||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNSDANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||  |||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAARGQVYFGIIAL 157


RESULT 18
AEB45466
ID   AEB45466 standard; protein; 157 AA.
XX
AC   AEB45466;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:50.
```

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XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45489.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 50; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||: :|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISKTYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 19
AEB45474
ID   AEB45474 standard; protein; 157 AA.
XX
AC   AEB45474;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:58.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45497.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 58; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
```

```
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    ||  ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRINHRYQDPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 20
AEB45457
ID   AEB45457 standard; protein; 157 AA.
XX
AC   AEB45457;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:41.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45480.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 41; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||: :|   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISSTYPDPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 21
AEB45475
ID   AEB45475 standard; protein; 157 AA.
XX
AC   AEB45475;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:59.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
```

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PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45498.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 59; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||:  |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISADYPHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 22
AEB45458
ID   AEB45458 standard; protein; 157 AA.
XX
AC   AEB45458;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:42.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45481.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 42; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||:  |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISKTYTHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
```

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Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 23
AEB45473
ID   AEB45473 standard; protein; 157 AA.
XX
AC   AEB45473;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:57.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45496.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 57; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||   | : ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITDRYSSPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 24
AEB45467
ID   AEB45467 standard; protein; 157 AA.
XX
AC   AEB45467;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:51.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45490.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 51; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
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CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||:  |:  ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISSHYRFPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 25
AEB45468
ID   AEB45468 standard; protein; 157 AA.
XX
AC   AEB45468;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:52.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45491.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 52; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  :|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITPAYPRPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 26
AEB45437
ID   AEB45437 standard; protein; 157 AA.
XX
AC   AEB45437;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:21.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
```

```
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45451.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 21; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match            95.8%;  Score 747;  DB 1;  Length 157;
  Best Local Similarity  92.4%;  Pred. No. 0;
  Matches  145;  Conservative    3;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| ||||||||||||||||||: ::   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISTTHNQPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 27
AEB45462
ID   AEB45462 standard; protein; 157 AA.
XX
AC   AEB45462;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:46.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45485.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 46; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match            95.8%;  Score 747;  DB 1;  Length 157;
  Best Local Similarity  93.0%;  Pred. No. 0;
```

```
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  :|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITSAYGPPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 28
AEB45470
ID   AEB45470 standard; protein; 157 AA.
XX
AC   AEB45470;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:54.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45493.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 54; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.8%;  Score 747;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITEQYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 29
AEB45456
ID   AEB45456 standard; protein; 157 AA.
XX
AC   AEB45456;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:40.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45479.
XX
```

```
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 40; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWKNAGANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||| :||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFASTGQVYFGIIAL 157


RESULT 30
AEB45459
ID   AEB45459 standard; protein; 157 AA.
XX
AC   AEB45459;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:43.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45482.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 43; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||:  |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISPLYPKPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 31
AEB45465
ID   AEB45465 standard; protein; 157 AA.
XX
AC   AEB45465;
XX
DT   22-SEP-2005  (first entry)
```

```
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:49.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45488.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 49; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||| | ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITHKYPQPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 32
AEB45463
ID   AEB45463 standard; protein; 157 AA.
XX
AC   AEB45463;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:47.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45486.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 47; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
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```
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| ||||||||||||||||||:  |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISRVYTAPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 33
AEB45429
ID   AEB45429 standard; protein; 157 AA.
XX
AC   AEB45429;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:13.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45443.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 13; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.4%;  Score 744;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||| |  |||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWSNPMANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||  ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFANPGQVYFGIIAL 157


RESULT 34
AEB45428
ID   AEB45428 standard; protein; 157 AA.
XX
AC   AEB45428;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:12.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
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```
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45442.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 12; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.3%;  Score 743;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    1;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWRNEHANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||  :||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFNNAGQVYFGIIAL 157


RESULT 35
AEB45425
ID   AEB45425 standard; protein; 157 AA.
XX
AC   AEB45425;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:9.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45439.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 9; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.3%;  Score 743;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    2;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWRNSHANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120
```

```
Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||: :||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFSGTGQVYFGIIAL 157


RESULT 36
AEB45421
ID   AEB45421 standard; protein; 157 AA.
XX
AC   AEB45421;
XX
DT   22-SEP-2005  (first entry)
XX
DE   Human TNF-alpha mutant protein, SEQ ID No:5.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45422.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Example 1; SEQ ID NO 5; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents human TNF-alpha mutant protein. Note: The sequence data for
CC   this patent did not form part of the printed specification, but was
CC   obtained in electronic format directly from WIPO at
CC   ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match            95.1%;  Score 742;  DB 1;  Length 157;
  Best Local Similarity  92.4%;  Pred. No. 0;
  Matches  145;  Conservative    0;  Mismatches   12;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  |||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWXNXXANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||    ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFXXXGQVYFGIIAL 157


RESULT 37
AEB45427
ID   AEB45427 standard; protein; 157 AA.
XX
AC   AEB45427;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:11.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45441.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 11; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
```

```
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.0%;  Score 741;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    1;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWHNNTANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| ||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||  :||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFDSNGQVYFGIIAL 157


RESULT 38
AEB45423
ID   AEB45423 standard; protein; 157 AA.
XX
AC   AEB45423;
XX
DT   22-SEP-2005  (first entry)
XX
DE   Human TNF-alpha mutant protein, SEQ ID No:7.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45424.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Example 1; SEQ ID NO 7; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents human TNF-alpha mutant protein. Note: The sequence data for
CC   this patent did not form part of the printed specification, but was
CC   obtained in electronic format directly from WIPO at
CC   ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.0%;  Score 741;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    0;  Mismatches   12;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| ||||||||||||||||||       ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIXXXXXXPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 39
AEB45435
ID   AEB45435 standard; protein; 157 AA.
XX
AC   AEB45435;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:19.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
```

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KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45449.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 19; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.0%;  Score 741;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    1;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||| :   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITPAINRPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
```

```
RESULT 40
AEB45426
ID   AEB45426 standard; protein; 146 AA.
XX
AC   AEB45426;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:10.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45440.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 10; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 146 AA;
```

```
  Query Match             89.5%;  Score 698;  DB 1;  Length 146;
  Best Local Similarity   93.8%;  Pred. No. 0;
  Matches  136;  Conservative    1;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| || ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWSNRYANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFA 145
              ||||||| |||||||||||||||:
Db        121 GGVFQLEPGDRLSAEINRPDYLDFS 145


Search completed: September 21, 2006, 14:40:08
Job time : 1 secs
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GenCore version 5.1.9

OM protein - protein search, using sw model

Run on: September 21, 2006, 09:09:19 ; Search time 0.001 Seconds
(without alignments)
1008.882 Million cell updates/sec

Title: US-10-668-178-2
Perfect score: 780
Sequence: 1 VRSSSRTPSDXPVAHVVANP.....RPDYLDFAESGQVYFGIIAL 157

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 41 seqs, 6426 residues

Total number of hits satisfying chosen parameters: 41

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 200 summaries

Database : xnotk.subdb:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	774	99.2	157	1	ADH10159	Human tumour necro
2	773	99.1	157	1	ADH10160	Human tumour necro
3	766	98.2	157	1	AEB45433	TNF-R1 specific hu
4	765	98.1	157	1	AEB45432	TNF-R1 specific hu
5	764	97.9	157	1	AEB45434	TNF-R1 specific hu
6	762	97.7	157	1	AEB45430	TNF-R1 specific hu
7	759	97.3	157	1	AEB45453	TNF-R2 specific hu
8	758	97.2	157	1	AEB45431	TNF-R1 specific hu
9	754	96.7	157	1	AEB45454	TNF-R2 specific hu
10	752	96.4	157	1	AEB45469	TNF-R2 specific hu
11	751	96.3	157	1	AEB45438	TNF-R1 specific hu
12	751	96.3	157	1	AEB45436	TNF-R1 specific hu
13	751	96.3	157	1	AEB45461	TNF-R2 specific hu
14	750	96.2	157	1	AEB45460	TNF-R2 specific hu
15	750	96.2	157	1	AEB45464	TNF-R2 specific hu
16	749	96.0	157	1	AEB45472	TNF-R2 specific hu
17	749	96.0	157	1	AEB45471	TNF-R2 specific hu
18	749	96.0	157	1	AEB45455	TNF-R2 specific hu
19	749	96.0	157	1	AEB45466	TNF-R2 specific hu
20	749	96.0	157	1	AEB45474	TNF-R2 specific hu
21	749	96.0	157	1	AEB45457	TNF-R2 specific hu
22	749	96.0	157	1	AEB45475	TNF-R2 specific hu
23	748	95.9	157	1	AEB45458	TNF-R2 specific hu
24	748	95.9	157	1	AEB45473	TNF-R2 specific hu
25	748	95.9	157	1	AEB45467	TNF-R2 specific hu
26	748	95.9	157	1	AEB45468	TNF-R2 specific hu
27	747	95.8	157	1	AEB45437	TNF-R1 specific hu
28	747	95.8	157	1	AEB45462	TNF-R2 specific hu
29	747	95.8	157	1	AEB45470	TNF-R2 specific hu
30	746	95.6	157	1	AEB45456	TNF-R2 specific hu
31	746	95.6	157	1	AEB45459	TNF-R2 specific hu
32	746	95.6	157	1	AEB45465	TNF-R2 specific hu
33	746	95.6	157	1	AEB45463	TNF-R2 specific hu
34	744	95.4	157	1	AEB45429	TNF-R1 specific hu
35	743	95.3	157	1	AEB45428	TNF-R1 specific hu
36	743	95.3	157	1	AEB45425	TNF-R1 specific hu
37	742	95.1	157	1	AEB45421	Human TNF-alpha mu
38	741	95.0	157	1	AEB45427	TNF-R1 specific hu
39	741	95.0	157	1	AEB45423	Human TNF-alpha mu
40	741	95.0	157	1	AEB45435	TNF-R1 specific hu
41	698	89.5	146	1	AEB45426	TNF-R1 specific hu

ALIGNMENTS

RESULT 1
ADH10159
ID ADH10159 standard; protein; 157 AA.
XX
AC ADH10159;
XX
DT 11-MAR-2004 (first entry)
XX
DE Human tumour necrosis factor variant protein.
XX
KW TNF; tumour necrosis factor; polyethylene glycol; cytostatic; cancer;
KW human; variant.
XX
OS Homo sapiens.
XX
FH Key Location/Qualifiers
FT Misc-difference 11
FT /label= Asp, Ala, Arg, Ser, Thr, Pro, Met or Leu
FT Misc-difference 65
FT /label= Asp, Ala, Arg, Ser, Thr, Pro, Met or Leu
FT Misc-difference 90
FT /label= Asp, Ala, Arg, Ser, Thr, Pro, Met or Leu
FT Misc-difference 98
FT /label= Asp, Ala, Arg, Ser, Thr, Pro, Met or Leu
FT Misc-difference 112
FT /label= Asp, Ala, Arg, Ser, Thr, Pro, Met or Leu
FT Misc-difference 128
FT /label= Asp, Ala, Arg, Ser, Thr, Pro, Met or Leu
XX
PN EP1354893-A2.
XX
PD 22-OCT-2003.
XX
PF 30-JAN-2003; 2003EP-00250587.
XX
PR 25-MAR-2002; 2002JP-00083509.
PR 26-JUN-2002; 2002JP-00185387.
XX
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU.
PA (MAYU/) MAYUMI T.
PA (TSUT/) TSUTSUMI Y.
PA (NAKA/) NAKAGAWA S.
XX
PI Mayumi T, Tsutsumi Y, Nakagawa S, Ikegami H;
XX
DR WPI; 2004-063952/07.
XX
PT A physiologically active complex which comprises a protein part with
PT tumor necrosis factor activity and a high molecular part has higher
PT stability and retention in living bodies and is useful to treat disease,
PT particularly cancer.
XX
PS Claim 2; SEQ ID NO 2; 18pp; English.
XX
CC The present sequence represents a physiologically active complex which
CC comprises a proteinaceous part with tumour necrosis factor (TNF) activity
CC and a high molecular part bound artificially to the N-terminus of the
CC proteinaceous part. The proteinaceous part comprises the sequence
CC selected from ADH10159 and the molecular part has a molecular weight of
CC 500-5000 Da and is a homopolymer of polyethylene glycol or a copolymer of

CC ethylene glycol and its derivatives. The invention is used to treat
CC susceptive disease, particularly cancer. The complex has a higher
CC stability and longer retention time in living bodies than intact tumour
CC necrosis factor. The present sequence represents a human TNF variant
CC protein.
XX
SQ Sequence 157 AA;

Query Match 99.2%; Score 774; DB 1; Length 157;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 157; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
Db 1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy 61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
Db 61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120

Qy 121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
Db 121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157

RESULT 2
ADH10160
ID ADH10160 standard; protein; 157 AA.
XX
AC ADH10160;
XX
DT 11-MAR-2004 (first entry)
XX
DE Human tumour necrosis factor variant protein.
XX
KW TNF; tumour necrosis factor; polyethylene glycol; cytostatic; cancer;
KW human; variant.
XX
OS Homo sapiens.
XX
PN EP1354893-A2.
XX
PD 22-OCT-2003.
XX
PF 30-JAN-2003; 2003EP-00250587.
XX
PR 25-MAR-2002; 2002JP-00083509.
PR 26-JUN-2002; 2002JP-00185387.
XX
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU.
PA (MAYU/) MAYUMI T.
PA (TSUT/) TSUTSUMI Y.
PA (NAKA/) NAKAGAWA S.
XX
PI Mayumi T, Tsutsumi Y, Nakagawa S, Ikegami H;
XX
DR WPI; 2004-063952/07.
DR N-PSDB; ADH10169.
XX
PT A physiologically active complex which comprises a protein part with
PT tumor necrosis factor activity and a high molecular part has higher
PT stability and retention in living bodies and is useful to treat disease,
PT particularly cancer.
XX
PS Example 1; SEQ ID NO 3; 18pp; English.
XX
CC The present sequence represents a physiologically active complex which
CC comprises a proteinaceous part with tumour necrosis factor (TNF) activity
CC and a high molecular part bound artificially to the N-terminus of the
CC proteinaceous part. The proteinaceous part comprises the sequence
CC selected from ADH10159 and the molecular part has a molecular weight of
CC 500-5000 Da and is a homopolymer of polyethylene glycol or a copolymer of
CC ethylene glycol and its derivatives. The invention is used to treat
CC susceptive disease, particularly cancer. The complex has a higher
CC stability and longer retention time in living bodies than intact tumour
CC necrosis factor. The present sequence represents a human TNF variant
CC protein.
XX
SQ Sequence 157 AA;

Query Match 99.1%; Score 773; DB 1; Length 157;
Best Local Similarity 96.2%; Pred. No. 0;
Matches 151; Conservative 0; Mismatches 6; Indels 0; Gaps 0;

Qy 1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
Db 1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy 61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
Db 61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy 121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
Db 121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157

RESULT 3
AEB45433
ID AEB45433 standard; protein; 157 AA.
XX
AC AEB45433;
XX
DT 22-SEP-2005 (first entry)
XX
DE TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:17.
XX
KW tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW vasotropic; cerebroprotective; dermatological; immunomodulator;
KW antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW mutein.
XX
OS Homo sapiens.
OS Synthetic.
XX
PN WO2005066206-A1.
XX
PD 21-JUL-2005.
XX
PF 05-JAN-2005; 2005WO-JP000032.
XX
PR 06-JAN-2004; 2004JP-00001427.
XX
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU.
PA (MAYU/) MAYUMI T.
PA (TSUT/) TSUTSUMI Y.
PA (NAKA/) NAKAGAWA S.
XX
PI Mayumi T, Tsutsumi Y, Nakagawa S, Ohta T;
XX
DR WPI; 2005-506850/51.
DR N-PSDB; AEB45447.
XX
PT Novel tumor necrosis factor TNF mutant protein, useful for treating
PT and/or preventing diseases such as inflammation, and other diseases
PT caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT rheumatoid arthritis, allergy.
XX
PS Claim 4; SEQ ID NO 17; 34pp; Japanese.
XX
CC The invention relates to tumor necrosis factor (TNF) mutant proteins,

```
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             98.2%;  Score 766;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    1;  Mismatches    7;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||: ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFADDGQVYFGIIAL 157


RESULT 4
AEB45432
ID   AEB45432 standard; protein; 157 AA.
XX
AC   AEB45432;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:16.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45446.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 16; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             98.1%;  Score 765;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    1;  Mismatches    7;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||| |:||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFRETGQVYFGIIAL 157


RESULT 5
AEB45434
ID   AEB45434 standard; protein; 157 AA.
XX
AC   AEB45434;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:18.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
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KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45448.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 18; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             97.9%;  Score 764;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    0;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||  ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFANDGQVYFGIIAL 157
```

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RESULT 6
AEB45430
ID   AEB45430 standard; protein; 157 AA.
XX
AC   AEB45430;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:14.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45444.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 14; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
```

```
SQ   Sequence 157 AA;

  Query Match             97.7%;  Score 762;  DB 1;  Length 157;
  Best Local Similarity   94.3%;  Pred. No. 0;
  Matches  148;  Conservative    2;  Mismatches    7;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||| ::||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFKDTGQVYFGIIAL 157


RESULT 7
AEB45453
ID   AEB45453 standard; protein; 157 AA.
XX
AC   AEB45453;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:37.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45476.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 37; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             97.3%;  Score 759;  DB 1;  Length 157;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches  149;  Conservative    0;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| || ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWQNRWANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 8
AEB45431
ID   AEB45431 standard; protein; 157 AA.
XX
AC   AEB45431;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:15.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
```

```
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45445.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 15; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             97.2%;  Score 758;  DB 1;  Length 157;
  Best Local Similarity   94.3%;  Pred. No. 0;
  Matches  148;  Conservative    0;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||   |||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFRTDGQVYFGIIAL 157


RESULT 9
AEB45454
ID   AEB45454 standard; protein; 157 AA.
XX
AC   AEB45454;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:38.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45477.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 38; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.7%;  Score 754;  DB 1;  Length 157;
  Best Local Similarity   94.3%;  Pred. No. 0;
  Matches  148;  Conservative    0;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWTNGYANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 10
AEB45469
ID   AEB45469 standard; protein; 157 AA.
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XX
AC   AEB45469;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:53.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45492.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 53; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.4%;  Score 752;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  ||   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITKSYSKPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 11
AEB45438
ID   AEB45438 standard; protein; 157 AA.
XX
AC   AEB45438;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:22.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45452.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 22; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
```

```
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.3%;  Score 751;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    ||  |||||||  |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIGGPYQRPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 12
AEB45436
ID   AEB45436 standard; protein; 157 AA.
XX
AC   AEB45436;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:20.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45450.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 20; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.3%;  Score 751;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    |  |||||||  |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAPGYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 13
AEB45461
ID   AEB45461 standard; protein; 157 AA.
XX
AC   AEB45461;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:45.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
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PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45484.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 45; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.3%;  Score 751;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    3;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
               |||| |||||||||||||||||: :| : ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISSAYASPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 14
AEB45460
ID   AEB45460 standard; protein; 157 AA.
XX
AC   AEB45460;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:44.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45483.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 44; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.2%;  Score 750;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
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Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||: :|   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISYNYNGPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 15
AEB45464
ID   AEB45464 standard; protein; 157 AA.
XX
AC   AEB45464;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:48.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45487.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 48; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.2%;  Score 750;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  :|   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITTAYSGPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 16
AEB45472
ID   AEB45472 standard; protein; 157 AA.
XX
AC   AEB45472;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:56.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45495.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 56; 34pp; Japanese.
```

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XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||: :|   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISKTYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 17
AEB45471
ID   AEB45471 standard; protein; 157 AA.
XX
AC   AEB45471;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:55.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45494.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 55; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||   | : ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITPGYPSPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 18
AEB45455
ID   AEB45455 standard; protein; 157 AA.
XX
AC   AEB45455;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:39.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
```

KW plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW vasotropic; cerebroprotective; dermatological; immunomodulator;
KW antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW mutein.
XX
OS Homo sapiens.
OS Synthetic.
XX
PN WO2005066206-A1.
XX
PD 21-JUL-2005.
XX
PF 05-JAN-2005; 2005WO-JP000032.
XX
PR 06-JAN-2004; 2004JP-00001427.
XX
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU.
PA (MAYU/) MAYUMI T.
PA (TSUT/) TSUTSUMI Y.
PA (NAKA/) NAKAGAWA S.
XX
PI Mayumi T, Tsutsumi Y, Nakagawa S, Ohta T;
XX
DR WPI; 2005-506850/51.
DR N-PSDB; AEB45478.
XX
PT Novel tumor necrosis factor TNF mutant protein, useful for treating
PT and/or preventing diseases such as inflammation, and other diseases
PT caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT rheumatoid arthritis, allergy.
XX
PS Claim 5; SEQ ID NO 39; 34pp; Japanese.
XX
CC The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC a TNF mutant protein comprising an amino acid sequence derived from the
CC human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC N-terminus, and amino acid residues at positions 84-89 by other amino
CC acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC protein. The TNF mutant proteins are useful for treating and/or
CC preventing diseases such as inflammation, and other diseases caused by
CC overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC The sequence data for this patent did not form part of the printed
CC specification, but was obtained in electronic format directly from WIPO
CC at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ Sequence 157 AA;

Query Match 96.0%; Score 749; DB 1; Length 157;
Best Local Similarity 93.6%; Pred. No. 0;
Matches 147; Conservative 0; Mismatches 10; Indels 0; Gaps 0;

```
Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              ||||||||| |||||||||||||||||  |||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNSDANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||  ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAARGQVYFGIIAL 157
```

RESULT 19
AEB45466
ID AEB45466 standard; protein; 157 AA.
XX
AC AEB45466;
XX
DT 22-SEP-2005 (first entry)
XX
DE TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:50.
XX
KW tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW vasotropic; cerebroprotective; dermatological; immunomodulator;
KW antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW mutein.
XX
OS Homo sapiens.
OS Synthetic.
XX
PN WO2005066206-A1.
XX
PD 21-JUL-2005.
XX
PF 05-JAN-2005; 2005WO-JP000032.
XX
PR 06-JAN-2004; 2004JP-00001427.
XX
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU.
PA (MAYU/) MAYUMI T.
PA (TSUT/) TSUTSUMI Y.
PA (NAKA/) NAKAGAWA S.
XX
PI Mayumi T, Tsutsumi Y, Nakagawa S, Ohta T;
XX
DR WPI; 2005-506850/51.
DR N-PSDB; AEB45489.
XX
PT Novel tumor necrosis factor TNF mutant protein, useful for treating
PT and/or preventing diseases such as inflammation, and other diseases
PT caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT rheumatoid arthritis, allergy.
XX
PS Claim 5; SEQ ID NO 50; 34pp; Japanese.
XX
CC The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC a TNF mutant protein comprising an amino acid sequence derived from the
CC human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC N-terminus, and amino acid residues at positions 84-89 by other amino
CC acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC protein. The TNF mutant proteins are useful for treating and/or
CC preventing diseases such as inflammation, and other diseases caused by
CC overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC The sequence data for this patent did not form part of the printed
CC specification, but was obtained in electronic format directly from WIPO

```
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||: :|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISKTYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 20
AEB45474
ID   AEB45474 standard; protein; 157 AA.
XX
AC   AEB45474;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:58.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45497.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 58; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.6%;  Pred. No. 0;
  Matches  147;  Conservative    0;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| ||||||||||||||||||    ||  ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRINHRYQDPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 21
AEB45457
ID   AEB45457 standard; protein; 157 AA.
XX
AC   AEB45457;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:41.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
```

```
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45480.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 41; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||: :|   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISSTYPDPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 22
AEB45475
ID   AEB45475 standard; protein; 157 AA.
XX
AC   AEB45475;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:59.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45498.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 59; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             96.0%;  Score 749;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||:  |   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISADYPHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 23
```

```
AEB45458
ID   AEB45458 standard; protein; 157 AA.
XX
AC   AEB45458;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:42.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45481.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 42; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              ||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||: :|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISKTYTHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 24
AEB45473
ID   AEB45473 standard; protein; 157 AA.
XX
AC   AEB45473;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:57.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45496.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 57; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
```

```
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||   | : ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITDRYSSPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 25
AEB45467
ID   AEB45467 standard; protein; 157 AA.
XX
AC   AEB45467;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:51.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45490.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 51; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    2;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||:  |:  ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISSHYRFPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 26
AEB45468
ID   AEB45468 standard; protein; 157 AA.
XX
AC   AEB45468;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:52.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
```

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PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45491.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 52; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.9%;  Score 748;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||| :|  ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITPAYPRPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 27
AEB45437
ID   AEB45437 standard; protein; 157 AA.
XX
AC   AEB45437;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:21.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45451.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 21; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.8%;  Score 747;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    3;  Mismatches    9;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
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```
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| ||||||||||||||||||: ::   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISTTHNQPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 28
AEB45462
ID   AEB45462 standard; protein; 157 AA.
XX
AC   AEB45462;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:46.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45485.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 46; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.8%;  Score 747;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| ||||||||||||||||||:|   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITSAYGPPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 29
AEB45470
ID   AEB45470 standard; protein; 157 AA.
XX
AC   AEB45470;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:54.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45493.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
```

```
XX
PS   Claim 5; SEQ ID NO 54; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.8%;  Score 747;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    |   |||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITEQYSHPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 30
AEB45456
ID   AEB45456 standard; protein; 157 AA.
XX
AC   AEB45456;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:40.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45479.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 40; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWKNAGANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||| :|||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFASTGQVYFGIIAL 157


RESULT 31
AEB45459
ID   AEB45459 standard; protein; 157 AA.
XX
AC   AEB45459;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:43.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
```

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KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45482.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 43; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||:  |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISPLYPKPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 32
AEB45465
ID   AEB45465 standard; protein; 157 AA.
XX
AC   AEB45465;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:49.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45488.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 49; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
```

```
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||    |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITHKYPQPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 33
AEB45463
ID   AEB45463 standard; protein; 157 AA.
XX
AC   AEB45463;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R2 specific human TNF-alpha mutant protein, SEQ ID No:47.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45486.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 5; SEQ ID NO 47; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R2. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.6%;  Score 746;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    1;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||:  |   ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRISRVYTAPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 34
AEB45429
ID   AEB45429 standard; protein; 157 AA.
XX
AC   AEB45429;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:13.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
```

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PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45443.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 13; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.4%;  Score 744;  DB 1;  Length 157;
  Best Local Similarity   93.0%;  Pred. No. 0;
  Matches  146;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWSNPMANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||  ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFANPGQVYFGIIAL 157


RESULT 35
AEB45428
ID   AEB45428 standard; protein; 157 AA.
XX
AC   AEB45428;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:12.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45442.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 12; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.3%;  Score 743;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    1;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWRNEHANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||  :||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFNNAGQVYFGIIAL 157
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RESULT 36
AEB45425
ID   AEB45425 standard; protein; 157 AA.
XX
AC   AEB45425;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:9.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45439.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 9; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match           95.3%;  Score 743;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    2;  Mismatches   10;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWRNSHANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| |||||||||||||||: :||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFSGTGQVYFGIIAL 157


RESULT 37
AEB45421
ID   AEB45421 standard; protein; 157 AA.
XX
AC   AEB45421;
XX
DT   22-SEP-2005  (first entry)
XX
DE   Human TNF-alpha mutant protein, SEQ ID No:5.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45422.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Example 1; SEQ ID NO 5; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
```

```
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents human TNF-alpha mutant protein. Note: The sequence data for
CC   this patent did not form part of the printed specification, but was
CC   obtained in electronic format directly from WIPO at
CC   ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.1%;  Score 742;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    0;  Mismatches   12;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWXNXXANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||   ||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFXXXGQVYFGIIAL 157


RESULT 38
AEB45427
ID   AEB45427 standard; protein; 157 AA.
XX
AC   AEB45427;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:11.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45441.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 11; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.0%;  Score 741;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    1;  Mismatches   11;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| |  ||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWHNNTANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||  :||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFDSNGQVYFGIIAL 157


RESULT 39
AEB45423
ID   AEB45423 standard; protein; 157 AA.
XX
AC   AEB45423;
XX
DT   22-SEP-2005  (first entry)
XX
DE   Human TNF-alpha mutant protein, SEQ ID No:7.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
```

```
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45424.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Example 1; SEQ ID NO 7; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents human TNF-alpha mutant protein. Note: The sequence data for
CC   this patent did not form part of the printed specification, but was
CC   obtained in electronic format directly from WIPO at
CC   ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.0%;  Score 741;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    0;  Mismatches   12;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||       ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIXXXXXXPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 40
AEB45435
ID   AEB45435 standard; protein; 157 AA.
XX
AC   AEB45435;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:19.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45449.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 19; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 157 AA;

  Query Match             95.0%;  Score 741;  DB 1;  Length 157;
  Best Local Similarity   92.4%;  Pred. No. 0;
  Matches  145;  Conservative    1;  Mismatches   11;  Indels    0;  Gaps    0;
```

```
Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||  :   ||||||| ||||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRITPAINRPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFAESGQVYFGIIAL 157
              ||||||| ||||||||||||||||||||||||||||||
Db        121 GGVFQLEPGDRLSAEINRPDYLDFAESGQVYFGIIAL 157


RESULT 41
AEB45426
ID   AEB45426 standard; protein; 146 AA.
XX
AC   AEB45426;
XX
DT   22-SEP-2005  (first entry)
XX
DE   TNF-R1 specific human TNF-alpha mutant protein, SEQ ID No:10.
XX
KW   tumor necrosis factor-alpha; TNF-alpha; TNF inhibitor; inflammation;
KW   autoimmune disease; tumor; transplant rejection; cardiovascular disease;
KW   acquired immune deficiency syndrome; severe acute respiratory syndrome;
KW   plasmodium infection; meningitis; hepatitis; Alzheimers disease;
KW   antiinflammatory; cytostatic; antirheumatic; antiarthritic; antiallergic;
KW   antipsoriatic; anti-HIV; antiarteriosclerotic; immunosuppressive;
KW   vasotropic; cerebroprotective; dermatological; immunomodulator;
KW   antimalarial; antibacterial; hepatotropic; neuroprotective; nootropic;
KW   mutein.
XX
OS   Homo sapiens.
OS   Synthetic.
XX
PN   WO2005066206-A1.
XX
PD   21-JUL-2005.
XX
PF   05-JAN-2005; 2005WO-JP000032.
XX
PR   06-JAN-2004; 2004JP-00001427.
XX
PA   (HAYB ) HAYASHIBARA SEIBUTSU KAGAKU.
PA   (MAYU/) MAYUMI T.
PA   (TSUT/) TSUTSUMI Y.
PA   (NAKA/) NAKAGAWA S.
XX
PI   Mayumi T,  Tsutsumi Y,  Nakagawa S,  Ohta T;
XX
DR   WPI; 2005-506850/51.
DR   N-PSDB; AEB45440.
XX
PT   Novel tumor necrosis factor TNF mutant protein, useful for treating
PT   and/or preventing diseases such as inflammation, and other diseases
PT   caused by overexpression of TNF, such as autoimmune diseases, tumor,
PT   rheumatoid arthritis, allergy.
XX
PS   Claim 4; SEQ ID NO 10; 34pp; Japanese.
XX
CC   The invention relates to tumor necrosis factor (TNF) mutant proteins,
CC   particularly tumor necrosis factor mutant proteins specific for TNF-R1 or
CC   TNF-R2 (SEQ ID Nos 19-22 and 37-59 respectively). The invention discloses
CC   a TNF mutant protein comprising an amino acid sequence derived from the
CC   human TNF-alpha protein (given as SEQ ID No: 1) by the substitution of
CC   one or more amino acid residues at 29, 31, 32, 145, 146 and 147 from the
CC   N-terminus, and amino acid residues at positions 84-89 by other amino
CC   acid residue(s). Also described are: (1) a TNF inhibitor comprising a TNF
CC   mutant protein; and (2) a TNF formulation comprising a TNF mutant
CC   protein. The TNF mutant proteins are useful for treating and/or
CC   preventing diseases such as inflammation, and other diseases caused by
CC   overexpression of TNF, such as autoimmune diseases, tumors (e.g. colon
CC   cancer, rectal cancer, uterine cancer, brain tumor, leukemia, lymphoma),
CC   Crohn's disease, rheumatoid arthritis, allergies, psoriasis, cachexia,
CC   transplant rejection, stroke, ischemia, restenosis, AIDS, severe acute
CC   respiratory syndrome (SARS), atherosclerosis, Behcet's disease, systemic
CC   lupus erythematosus, malaria, meningitis, hepatitis, Alzheimer's disease,
CC   etc. The TNF mutant proteins are highly stable in vivo. This sequence
CC   represents a human TNF-alpha mutant protein specific for TNF-R1. Note:
CC   The sequence data for this patent did not form part of the printed
CC   specification, but was obtained in electronic format directly from WIPO
CC   at ftp.wipo.int/pub/published_pct_sequences.
XX
SQ   Sequence 146 AA;

  Query Match             89.5%;  Score 698;  DB 1;  Length 146;
  Best Local Similarity   93.8%;  Pred. No. 0;
  Matches  136;  Conservative    1;  Mismatches    8;  Indels    0;  Gaps    0;

Qy          1 VRSSSRTPSDXPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS 60
              |||||||||| |||||||||||||||| || |||||||||||||||||||||||||||||
Db          1 VRSSSRTPSDMPVAHVVANPQAEGQLQWSNRYANALLANGVELRDNQLVVPSEGLYLIYS 60

Qy         61 QVLFXGQGCPSTHVLLTHTISRIAVSYQTXVNLLSAIXSPCQRETPEGAEAXPWYEPIYL 120
              |||| |||||||||||||||||||||||| ||||||| |||||||||||| ||||||||
Db         61 QVLFSGQGCPSTHVLLTHTISRIAVSYQTPVNLLSAIRSPCQRETPEGAEANPWYEPIYL 120

Qy        121 GGVFQLEXGDRLSAEINRPDYLDFA 145
              ||||||| |||||||||||||||:
Db        121 GGVFQLEPGDRLSAEINRPDYLDFS 145


Search completed: September 21, 2006, 09:09:21
Job time : 1 secs
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